PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 06 December 1999 (06.12.99)	
International application No. PCT/CA99/00287	**Applicant's or agent's file reference** 1038-937 MIS
International filing date (day/month/year) 01 April 1999 (01.04.99)	**Priority date** (day/month/year) 07 April 1998 (07.04.98)
Applicant SIA, Charles, D., Y. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

02 November 1999 (02.11.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer J.M. Vivet
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

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UZ	Uzbekistan
VN	Viet Nam
YU	Yugoslavia
ZW	Zimbabwe

INTERNATIONAL SEARCH REPORT

Ir. ational Application No
PCT/CA 99/00287

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K39/21 A61K39/29 A61K39/39 C07K14/16 //(A61K39/29, 39:21)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 22317 A (CYTEL CORPORATION) 24 August 1995 (1995-08-24) examples 4,15 claims	1-6,8,9, 11
Y		7,10, 12-15

Y	C. VAN BAALEN ET AL.: "Human immunodeficiency virus type 1 Rev- and Tat-specific cytotoxic T lymphocyte frequencies inversely correlate with rapid progression to AIDS." JOURNAL OF GENERAL VIROLOGY, vol. 78, no. 8, August 1997 (1997-08), pages 1913-1918, XP002112914 abstract table 2	7,10, 12-15

	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 August 1999	03/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Nooij, F

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 99/00287

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 534 618 A (THE SCRIPPS RESEARCH INSTITUTE) 31 March 1993 (1993-03-31) the whole document	1-15
A	EP 0 534 615 A (CYTEL CORPORATION) 31 March 1993 (1993-03-31) example V claims	1-15
A	V. BLAZEVIC ET AL.: "Helper and cytotoxic T cell responses of HIV type 1-infected individuals to synthetic peptides of HIV type 1 Rev." AIDS RESEARCH AND HUMAN RETROVIRUSES, vol. 11, no. 11, November 1995 (1995-11), pages 1335-1342, XP000566753 abstract	1-15
A	B. DEPREZ ET AL.: "Comparative efficiency of simple lipopeptide constructs for in vivo induction of virus-specific CTL." VACCINE, vol. 14, no. 5, April 1996 (1996-04), pages 375-382, XP002112915 Oxford, GB the whole document	1-15

1

INTERNATIONAL SEARCH REPORT

...ernational application No.
PCT/CA 99/ 00287

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-11
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 99/00287

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9522317 A	24-08-1995	AU	1847395 A	04-09-1995
		AU	2500499 A	24-06-1999
		CA	2183416 A	24-08-1995
		EP	0804158 A	05-11-1997
EP 534618 A	31-03-1993	AU	679901 B	17-07-1997
		AU	2540892 A	16-03-1993
		BG	98522 A	31-05-1995
		CA	2115927 A	04-03-1993
		CZ	9400428 A	15-02-1995
		FI	940919 A	25-04-1994
		HU	67529 A	28-04-1995
		JP	6510050 T	10-11-1994
		NO	940661 A	19-04-1994
		NZ	244102 A	20-12-1996
		NZ	270625 A	20-12-1996
		OA	9889 A	15-09-1994
		WO	9303753 A	04-03-1993
		US	5780036 A	14-07-1998
		US	5840303 A	24-11-1998
		ZA	9206440 A	07-06-1993
EP 534615 A	31-03-1993	AU	687725 B	05-03-1998
		AU	2548792 A	16-03-1993
		BG	98523 A	31-05-1995
		CA	2115839 A	04-03-1993
		CZ	9400427 A	16-11-1994
		FI	940918 A	08-04-1994
		HU	68510 A	28-06-1995
		JP	6510051 T	10-11-1994
		NO	940660 A	22-04-1994
		NZ	244103 A	27-07-1997
		NZ	270605 A	27-07-1997
		OA	9888 A	15-09-1994
		WO	9303764 A	04-03-1993
		ZA	9206441 A	07-06-1993

PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

STEWART, Michael I.
Sim & McBurney
330 University Avenue
6th Floor
Suite 600
Toronto, Ontario M5G 1R7
CANADA

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	11.07.2000
Applicant's or agent's file reference 1038-937 MIS	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA99/00287	01/04/1999	07/04/1998

Applicant
CONNAUGHT LABORATORIES LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Digiusto, M Tel.+49 89 2399-8162

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
1038-937 MIS		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA99/00287	01/04/1999	07/04/1998
International Patent Classification (IPC) or national classification and IPC A61K39/21		
Applicant CONNAUGHT LABORATORIES LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02/11/1999	11.07.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Weijland, A Telephone No. +49 89 2399 7490

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/00287

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-18 as originally filed

Claims, No.:

1-15 as originally filed

Drawings, sheets:

1/9-9/9 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-11.

because:

☒ the said international application, or the said claims Nos. 1-11 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☒ the claims, or said claims Nos. 1-11 are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-5, 8-15
	No:	Claims	1, 2, 6, 7 No
Inventive step (IS)	Yes:	Claims	13-15
	No:	Claims	1-12
Industrial applicability (IA)	Yes:	Claims	12-15
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

The following documents (D) are referred to in this opinion; the numbering will be adhered to the rest of the procedure:

D1: WO 95 22317 A (CYTEL CORPORATION) 24 August 1995 (1995-08-24)
D2: V. BLAZEVIC ET AL.: 'Helper and cytotoxic T cell responses of HIV type 1-infected individuals to synthetic peptides of HIV type 1 Rev.' AIDS RESEARCH AND HUMAN RETROVIRUSES, vol. 11, no. 11, November 1995 (1995-11), pages 1335-1342
D3: B. DEPREZ ET AL.: 'Comparative efficiency of simple lipopeptide constructs for in vivo induction of virus-specific CTL.' VACCINE, vol. 14, no. 5, April 1996 (1996-04), pages 375-382

SECTION III

1.1 For the assessment of the present claims 1-11 on the question whether they are industrially applicable, no unified criteria exist in the PCT contracting states. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in a medical treatment and the use of such compound for the manufacture of a medicament for new medical treatment.

In the above mentioned context the passage in claims 1 "administering to the host a T-helper molecule" and "subsequently administering to the host a mixture" is considered to cover treatment by therapy.

Therefore, claims 1-11 relate to the subject-matter considered by this authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

1.2 In the present case it is not reasonable to predict that all variants covered by claim 1 (i.e. all possible combinations of T-helper cell molecules and T-cell inducing HIV-derived molecules) have the properties (generating of CTL response) the application ascribes to them.

This is apparent from page 8 (lines 29-33) of the description, where it is disclosed that A2Kb transgenic animals primed with CLP-243 and subsequently with CLP-243 and CPL-164, do not show a specific effector response. Moreover, on page 9 (lines 7-14) of the description is disclosed that when A2Kb transgenic mice are treated with CLP-176, CLP-175 or CLP-164 (without CLP-243 priming) no effective CTL response is observed. Thus, the subject matter of claims 1-11 is a not allowed generalization from particular examples and is not supported by the description.

Moreover, it is clear from the description (page 8 (line 17) to page 9 (line 15)) that the following features are essential to the definition of claims 1:

(1) CLP-243 (to prime T-helper cells)
(2) CPL-243 and CLP-175/CLP-176 (to generate an HIV-specific CTL response)

Since independent claim 1 does not contain these features it does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.

SECTION V

2. Novelty

2.1 D1 (abstract; example 15, page 7 first paragraph;) describes CTL responses that are effectively induced to viral antigens by using CTL-inducing peptides, adjuvants or lipidated peptides. A treatment of humans with HIV-1 infections by inducing specific CTLs is disclosed. The T-helper cell molecules can be linked or unlinked to the CTL antigens and delivered in an adjuvant such as alum. Typically, the lipid is linked at the N-terminus of the helper T lymphocyte (HTL)-inducing peptide, optionally including a spacer, and is linked at the C-terminus to a CTL inducing peptide. Claim 1 differs from D1 in that claim 1 describes two subsequent administration steps in which the first one comprises only a T-helper cell molecule and the second step in addition a T-cell inducing molecule.

2.2 Not withstanding the objections made under Article 6 PCT (see **SECTION III**, point 1.2 above), the subject matter of claims 1, 2, 6, 7 is not novel and does not meet the requirements of Article 33(2) PCT.

The subject matter of claim 1, relating to an HIV-1 specific CTL response by administering to the host subsequently a T cell helper molecule and a combination of a T-helper cell molecule and a T-cell inducing HIV-derived molecule, is anticipated by D2. D2 (abstract; Table 1; page 1340, right column, third paragraph) describes antigenic peptides identified on HXB2 HIV-1 regulatory protein Rev. Four synthetic peptides derived from the Rev sequence were shown to stimulate T helper cell (T-helper molecule in claim 1) proliferation in peripheral blood lymphocytes from HIV-seropositive individuals. The same peptides induced specific cytotoxic T lymphocyte (CTL) activities to target cells (T-helper molecule and T-cell inducing HIV-derived molecule in claim 1). The four peptides are situated within the first three amino-terminal HLA binding regions and are considered as antigens for CTL. It is suggested that successful antiviral vaccines need to include antigens that will stimulate both helper cells and CTLs (a method of generating an HIV-specific cytotoxic T-cell response). The proliferative response was inhibited by anti CD4 antibodies, showing that the proliferating cells were CD4+ T cells, i.e. MHC class II-restricted T cells. Claims 2, 6, 7 are also anticipated by D1 (see above).

2.2 The subject matter of claims 3-5, 8-11 and 12-15 is novel (Article 33(2) PCT).

The subject matter of claims 3-5, 8-11, relating to methods for generating an HIV-specific CTL response, is not disclosed in the prior art documents.

Claim 12, relating to a fragment corresponding to amino acids 52 to 116 of the Rev protein of HIV-1 LAI or the corresponding sequence from another HIV-1 isolate, is not disclosed in the prior art documents. The same applies to the subject matter of claims 13-15.

3. Inventive Step

3.1 In view of the objections raised under **SECTION III** (point 1.2) no positive

statement for the present set of claims 1-11 can be made.

3.2 The subject matter of claim 12 does not involve an inventive step (Article 33(3) PCT).

In view of the objections raised under **SECTION III**, the subject-matter of claim 12 would not appear to solve, within the disclosure of the present application, a technical problem. This is apparent from page 8 (lines 29-33) of the present description, where it is disclosed that A2Kb transgenic animals primed with CLP-243 and subsequently with CLP-243 and CPL-164, do not show a specific effector response.

3.3 The subject matter of claims 13-15 would appear to involve an inventive step (Article 33(3) PCT).

Claims 13-15, relating to lipopeptides, are not suggested in the prior art documents.

SECTION VII

4. Claim 7 is probably meant to be dependent on claim 6.

5. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 to D3 is not mentioned in the description, nor are these documents identified therein.

6. The phrase "and incorporated by reference..." as mentioned e.g. on page 2 (line 2) contravenes the requirement that the application needs to be self contained (see further Guidelines C-II 4.17).

7. The terms "63 to 73" and "74 to 83" in claim 12 are inconsistent with page 4 (lines 12-14) of the description and the sequence listing that mentions "65 to 75" and "78 to 87" respectively (Article 6 PCT).

SECTION VIII

9. The use of the bracketed terms "SEQ ID NO: 10" in claim 4, "SEQ ID NO: 9", "SEQ ID NO: 3", "SEQ ID NO: 5", "SEQ ID NO: 8" in claim 12 is considered to be entirely optional and therefore renders the scope the claims unclear (Article 6 PCT).

10. The terms "CLP-175 or CLP-176" in claims 10 and 15 are technically meaningless without reference to a sequence identity number and therefore the requirements of Article 6 PCT are not met.